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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,607	02/24/2004	Avi Ashkenazi	P1216R1C1D5	3220

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GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/785,607	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-54 and 56-59* is/are rejected.

7)☒ Claim(s) *55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 49-59 are pending and under examination as they read on an isolated polypeptide molecule comprising the amino acids of SEQ ID NO: 9 with or without the signal peptide and a chimeric polypeptide thereof.

2. According to the priority statement of 2/24/04, Applicant claims priority to U.S.-provisional application 60,066,364,PCT applications no. PCT/US98/24855 and PCT/US98/19437 and U.S. applications 09/953,499 and 09/254,465. Based on information given by applicant and an inspection of the patent applications, the examiner has concluded that the subject matter defined in this application is supported by the disclosure in U.S. Patent Applications 09/953,499, filed 9/14/2001 and 09/254,465, filed 3/5/1999; and PCT application PCT/US98/24855 (published as WO-9927098) filed 11/20/1998 but not supported by the others, for the following reasons: U.S provisional 60/066,364 does not disclose the amino acid sequence of PRO245. PCT/US98/19437 filed 9/17/1998, discloses the DNA and the amino acid sequence of PRO245. However, only the three priority applications listed above disclose an enabled use for PRO245, namely, that it inhibits VEGF stimulated proliferation of endothelial cells or induces apoptosis in endothelial cells. Accordingly, the subject matter defined in claims 49-59 has an effective filing date of 11/20/1998.

Should the applicant disagree with the Examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 11/20/1998 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession and fully enabled of prior to 11/20/1998.

3. The specification on page 1 should be amended to reflect the status of parent application No. 09/953,499 and 09/254,465.

4. Applicant's IDS, filed 6/7/04, is acknowledged. Only the references initiated were found in the parent applications 09/953,499 and 09/254,465. The BLAST results provided as reference Nos. 15-17 are not appropriate for an IDS. BLAST alignments should be appended as part of each individual sequence reference, which must include the Accession No., Database and earliest available date of the reference sequence in order to be appropriate for inclusion in the IDS.

5. The U.S. Patent 6,838,554 and 6,410,708 cited on the PTO FORM 892 is issued from the parental application serial No. 09/953,499 and 09/254,465, respectively.

6. There is a discrepancy in the length of SEQ ID NO: 11. Figure 5 shows that SEQ ID NO: 11 is a 1842 nucleotide sequence. The sequence listing indicates that SEQ ID NO:11 is a 2181 nucleotide sequence. Further, the specification on page 49, lines 36-40, discloses that clone DNA40628 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 52-54 (FIG. 5; SEQ ID NO: 11). The sequence listing SEQ ID NO:11 does

not correspond with the translation initiation site at nucleotide positions 52-54. Clarification is required.

7. The specification is objected to for failing to provide a brief description of each individual Figure. Figure 1 has panels labeled A and B that must be identified in the Brief Description of the Drawings as "Figures 1A and 1B", after which each individual panel must be separately described. Similarly, figures 9 and 10. Correction is required.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 49 and 53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases "having at least 80%/99% amino acid sequence identity" claimed in claims 49 and 53, lines 1-2, respectively, represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 2/24/04 points to the specification on page 12, lines 9-10 and 23-33 for support for the newly added limitations "having at least 80%/99% amino acid sequence identity" as claimed in claims 49 and 53, respectively. However, the specification does not provide a clear support of these limitations. It is noted that the specification on page 12, lines 24-36 indicates that variants of PRO301, not PRO245. Further, no 99% amino acid sequence identity is disclosed in the specification. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

10. Claims 49(c)-54(c) and 57-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the plasmid DNA35638-1141containting the cDNA encoding the polypeptide of SEQ ID NO: 9 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the

specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the plasmid, may satisfy first paragraph. See 37 CFR 1.801-1.809.

The amendment to the specification on page 68, filed 2/24/04, to assure that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, is acknowledged. However, in order to be fully compliant with the requirement, applicants must state that the deposit will be maintained for a term of at lest 30 years *and at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository.* See 37 C.F.R. 1.806.

11. Claims 49-54, 56 and 58-59 are rejected under 35 U.S.C 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising SEQ ID NO: 9 or an isolated polypeptide molecule having at least 80% amino acid sequence identity the amino acid sequence of SEQ ID NO: 9 for the inhibition of VEGF stimulated proliferation of endothelial cells, does not reasonably provide enablement for any an isolated polypeptide molecule "having at least 80%, 85%, 90%, 95% or 99% amino acid sequence identity" to: (a) the amino acid sequence of the polypeptide of SEQ ID NO:9, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 9, lacking its associated signal peptide claimed in claims 49-53; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209265 in claim 49(c)-53(c); an isolated polypeptide molecule comprising the amino acid sequence of the polypeptide of SEQ ID NO:9, lacking its associated signal peptide in claims 54(b) and 56. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The claims are directed to isolated polypeptide molecule having at least having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO: 9, a polypeptide sequence of SEQ ID NO:9 with or without its signal peptide. Dependent claims are directed to a chimeric polypeptide comprising the polypeptide of SEQ ID NO: 9 with or without its signal peptide. There is no functional limitation in the claims. Applicants have taught the polypeptide consisting of SEQ ID NO: 9 (fig. 11). The polypeptide was shown to have the activity of inhibiting VEGF stimulated proliferation of endothelial cells (pp.53, Example 4) or induces endothelial cell apoptosis (pp. 57, Example 10).

The claimed amino acids are described at least in part in terms of the percent % homology, the scope of the protein itself must be considered: The specification discloses that PRO245 has

significant homology to both A33 antigen and JAM (see pp. 19, lines 37-38). Further the specification, on page 12, lines 9-10 discloses that the PRO245 polypeptide is 312 amino acids long. The specification on page 53, under example 4, discloses the use of the protein of SEQ ID NO:9 in the inhibition of VEGF stimulated proliferation of endothelial cells growth.

The claims encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. The specification discloses that the polypeptide of SEQ ID NO: 9 shares homology with identity with junctional adhesion molecule (JAM). JAM is involved in the recruitment of monocytes in response to MCP-1, MCP-3 and LPS in vivo. Antibodies to JAM block monocyte transmigration in vivo. JAM is localized to the murine epithelia and endothelia as a junctional adhesion molecule for monocyte transmigration (page 42, lines 23-42). The art recognizes that there is great functional diversity among proteins in this class, and that the functions are not yet well known. Tsukita *et al* (Nat Rev Mol Cell Biol. 2(4):285-293, 2001) teach the multifunctional strands in tight junction and that JAM was shown to be involved in cell-cell adhesion/junctional assembly of epithelial/endothelial cells as well as in the extravasation of monocytes through endothelial cells, but our knowledge on its function is still fragmentary (see page 287, 1st col., 2nd ¶). Tsukita *et al* concluded that the picture of the molecular architecture of tight junctions remains incomplete, and other important constituents need to be identified. Further development of the molecular biology of tight junctions will lead to a better understanding of their functions, not only in normal physiology, but also in disease (page 292, last ¶). Therefore, knowledge of one JAM's structure and function does not provide predictability about function of a structurally related JAM, even within the same class. There are great diversity and uncertainty of function.

Also, at issue is whether claimed SEQ ID NO: 9 would have an associated signal peptide or not as claimed in claims 49(b)-54(b), 56. The specification fails to locate the signal peptide cleavage site. Palmeri *et al* (J Biol Chem. 2000 Jun 23;275(25):19139-45) teaches that VE-JAM (claimed SEQ ID NO: 9) is highly localized to the intercellular boundaries of endothelial cells (see abstract). The skilled in the art would conclude that VE-JAM is not a secreted protein and therefore would not contain the secretion signal peptide.

There are no working examples of polypeptides less than 100% identical to the polypeptide of SEQ ID NO: 9. There are three examples in which PRO245 was alleged to have activity: inhibition of VEGF stimulated endothelial cell proliferation (Example 4, page 53); stimulation and inhibition activity in mixed lymphocyte reactions (MLR) assays (Example 5, pages 54-55), induction of endothelial cell apoptosis (Example 10, pp. 57-58). The MLR results are contradictory and do not provide the skilled artisan with guidance for how to use the polypeptide. The results of inhibition of VEGF stimulated endothelial cell proliferation and induction of endothelial cell apoptosis do provide the skilled artisan with guidance for how to use the polypeptide. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification unless they possessed the activities of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells, as disclosed in the instant specification. While the specification generally describes properties of JAM proteins, it is acknowledged that such proteins are diverse in

function and structure (See Tsukita *et al*, supra.). The specification does not provide guidance for using polypeptides related to (i.e., 80%-99% identity) but not identical to at least amino acids of SEQ ID NO: 9 which do not have one of the specific disclosed activities shown for PRO245. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of JAM proteins and lack of knowledge about function(s) of encompassed polypeptides structurally related SEQ ID NO:9, the one limited working example of PRO245 polypeptide and its one function, the lack of direction or guidance for using polypeptides that are not identical to SEQ ID NO:9, and the breath of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

12. Claims 49-54, 56 and 58-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence with or without its associated signal peptide. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity. Further, the claims are drawn to a polypeptide that is lacking the associated signal peptide.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 9. No active variants or signal peptide cleavage site are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQZd 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical* Co. Ltd., 18 USPQZd 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQZd 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 9, but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. The following rejections under 35 U.S.C 102 and 103 are made under the assumption that the effective date for the instant claimed invention is 11/20/1998.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

15. Claims 49-51 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 98/40483 (9/17/1998).

The '483 publication teaches a polypeptide molecule having 91% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO: 9 (see page 34, last row, published SEQ ID NO: 75, page 25, line 22 through page 26 line 11 in particular).

The reference teachings anticipate the claimed invention.

16. Claims 49-51 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Pat. No. 6,448,230.

The '230 patent teaches a polypeptide molecule having 91% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO: 9 (see Fig. 1F, last row, referenced SEQ ID NO: 76, col., 28, line 57 through col. 29 line 29 in particular).

The reference teachings anticipate the claimed invention.

17. No claim is allowed.

18. Claim 55 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 21, 2005

Maher Haddad

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600